REMARKS/ARGUMENTS

Claims 124, 129-131, 135-150 were pending in this application. Claims 146-148 are canceled without prejudice or disclaimer. Claims 149-150 have been amended to recite the functional recitation, "wherein the polypeptide encoded by said nucleic acid enhances the uptake of glucose or FFA (free fatty acids) by adipocyte cells," support for which is found in the instant specification in Example 158, page 530, lines 13-15". These claims have also been amended to correct claim dependencies. No new matter is added by way of these amendments and their entry is respectfully requested.

The rejections to the presently pending claims 124, 129-131, 135-145 and 149-150 are respectfully traversed.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 124, 129-131, 135-150 stand rejected under 35 U.S.C. §101 for lack of utility.

Claims 124, 129-131, 135-150 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly since "the claimed invention was not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

The Examiner continues to maintain the rejections based on the gene amplification assay (pages 3-6 of the instant Office action). But, without acquiescing to the propriety of those rejections, mainly in the interest of expediting prosecution in this case, Claims 146-148 have been canceled without prejudice or disclaimer and hence rejections to these claims are rendered moot. Therefore, instead of the gene amplification assay, the instantly pending claims only rely upon assay 94 or 'the glucose/FFA uptake assay,' (Example 158) for patentable utility of nucleic acids encoding PRO1182 polypeptides. Accordingly, any of the Examiner's rejections /references or discussions referring to the gene amplification assay are not currently addressed. For the reasons outlined below, Applicants respectfully traverse this rejection with respect to Claims 124, 129-131, 135-145 and 149-150.

Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO1182 gene possesses a credible, specific and substantial asserted utility and is fully enabled, based on the utility for PRO1182 as a stimulator

of the adipocyte glucose/FFA Uptake Assay. Accordingly, the nucleic acids encoding PRO1182 also have utility.

A. PRO1182 is a *Stimulator* of Glucose and/or FFA Uptake

Previously, Applicants had erroneously referred to PRO1182 as a molecule that inhibits glucose/FFA uptake by adipocytes. Instead, as discussed below, PRO1182 enhances glucose/ FFA uptake by adipocytes. Support for this amendment is clearly present in Example 158, which discloses the glucose/ FFA uptake assay as follows:

> Primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again.

As a control, identical incubations and samplings were performed on cells that were incubated overnight in media, initially supplemented with insulin rather than the PRO1182 polypeptide. Results were scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. As PRO1182 resulted in more than 1.5 times the uptake of the insulin control, PRO1182 tested positive as a **stimulator** of (or enhanced) glucose/FFA uptake in adipocyte cells (specifically, see Example 158).

Applicants had submitted supportive references, Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), to show that, the utility for agents modulating glucose/FFA uptake was well known in the art at the time of filing of the instant application, for instance, in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia. Therefore, one skilled in the art would have known how to use PRO1182 in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia, based on the glucose/FFA uptake assay results for PRO1182. Accordingly, the nucleic acids encoding PRO1182 are also useful.

In the recent Office action, the Examiner herself acknowledges the teachings of the articles by the Applicants, indicating that "each of the references cited by Applicants teaches that the agents utilized in the assays *enhance* glucose uptake.....**Disorders such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized by a reduction in the amount of glucose entering all cells, including adipocytes.....Therefore, as emphasized by Tafuri et al., Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), one skilled in the art is searching for agents that will enhance glucose uptake into adipocyte cells**." (page 7, line 3 through page 8, line 5).

Therefore, based on the instant results demonstrating the ability of the PRO1182 polypeptides to enhance glucose uptake in the glucose/ FFA assay, one skilled in the art, as the Examiner acknowledges, would readily recognize that PRO1182 polypeptides and the nucleic acids encoding them are useful in the treatment of disorders benefiting from this biological activity, such as obesity, diabetes, or hyper- or hypo-insulinemia.

The Examiner however maintained the previous rejection on page 8 of the Office action and says "Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000) teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification....None of the references utilizes the same grading scale disclosed in the instant specification, but instead report dose-response curves. The instant specification does not report any specific cell numbers or statistical differences and there is no indication in the specification as to how PRO1182 inhibited glucose uptake as compared to control or whether the results were significant." The Examiner concludes that the PRO1182 peptide is not in currently available form, and the asserted utility is not substantial. Applicants once again strongly disagree with the utility standards utilized by the Examiner in this rejection.

Applicants respectfully submit that, compliance with the utility requirement does not require that the methodology used in making the invention be the same as those used in the referenced or related art. What is important is that the assay be a well- recognized assay and that guidelines be provided in the specification to perform the assay, including assay read-out, if applicable. As discussed in their response dated January 20, 2006, Applicants submitted that the glucose uptake assay is a well-accepted assay in the art for identifying molecules that modulate

glucose uptake. The fact remains that the results of the adipocyte glucose/FFA uptake assay were positive, indicating that PRO1182 polypeptides and the nucleic acids encoding them are useful in *enhancing* glucose uptake by adipocyte cells. The instant specification also clearly discusses the controls used in the assay. For example, the results of the glucose uptake assay were scored as positive if the uptake was greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. Since PRO1182 resulted in more than 1.5 times the uptake of the insulin control, PRO1182 tested positive as a **stimulator** (or enhancer) of glucose/FFA uptake in adipocyte cells.

The Examiner's requirement for specific "cell numbers and statistical results" are also clearly not a requirement of the utility standards set by the USPTO. Applicants submit that the glucose uptake assay described herein is a comparative assay, meaning that the utility is based upon a comparison of relative uptake levels between a well-accepted and known control like insulin (for glucose uptake) and a test molecule like PRO1182. Useful pharmacological information is obtained when a relative difference is observed in this assay. In addition, the need for "cell numbers or statistical results" is a misplaced requirement, and is a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a pharmacological or diagnostic assay, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new assay, will indeed ask for actual numerical data, statistical analysis, and other specific information before any assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the nucleic acids encoding the polypeptide PRO1182 of Claims 124, 129-131, 135-145 and 149-150. The nucleic acids encoding PRO1182 polypeptides are in currently available form, and the asserted utility is specific, credible and substantial. Further, based on this utility, the disclosure in the specification, the well-established knowledge in the art (at the effective date of filing) regarding

agents that modulate or regulate glucose uptake and their usefulness in treatment of metabolic diseases, one skilled in the art would have known how to make and use the claimed nucleic acids.

Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

Claim Rejections - 35 U.S.C. §112, First Paragraph - Written Description

Claims 146-150 remain rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description. In particular, the Examiner maintains that Applicants have not "described or shown possession of all polynucleotides 80-99% homology to SEQ ID NO:356, that still retain the function of SEQ ID NO:356." (page 10 of Office action).

Claims 146-148 have been canceled without prejudice or disclaimer. For the reasons outlined below, Applicants maintain that claims 149-150 which are directed to nucleic acids with 95-99% sequence identity to SEQ ID NO: 356 are adequately described in the specification as filed.

Arguments

The legal standards for evaluating Written Description was discussed in the previous response. Briefly, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The currently amended claims claim the genus of nucleic acids with at least 95-99% sequence identity to SEQ ID NO:357 with the functional recitation: "wherein the polypeptide encoded by said nucleic acid **enhances** the uptake of glucose or FFA (free fatty acids) by adipocyte cells," support for which is found in the instant specification in Example 158, page 530, lines 13-15." The amended claims now recite the functional recitation: "the polypeptide encoded by said nucleic acid **enhances** the uptake of glucose or FFA (free fatty acids) by adipocyte cells" which, **as acknowledged by the Examiner** and discussed above, is based on a well-established assay known to the skilled artisan at the effective filing date of this application.

Therefore, the claimed nucleic acids are defined both by functional as well as structural features. Moreover, the instant invention evidences the actual reduction to practice of full-length PRO1182 of SEQ ID NO: 357, the nucleic acid encoding PRO1182 (SEQ ID NO: 356) and the nucleic acid deposited under ATCC accession number 203088 that encodes PRO1182.

The present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials which analyzes a claim directed to a protein and variants thereof having 95% sequence identity, all of which share the same biological function, for its compliance with the written description requirement of 35 U.S.C. §112, first paragraph. The Written Description Training Materials conclude that such a claim satisfies the written description requirement of 35 U.S.C. §112, first paragraph, when: (1) a single protein sequence is actually reduced to practice, (2) procedures for making variants of that "reduced to practice" protein sequence are conventional in the art, and (3) an assay is described which allows identification of other proteins having the same biological activity. The reasoning provided by the USPTO in the Written Description Training Materials is that:

> "[t]here is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:...does not have substantial variation since all of the variants must possess the specified [biological function] and must have at least 95% identity to the reference sequence, SEQ ID NO:...The single species disclosed ***is representative of the genus*** because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:...which are capable of the specified [biological function]. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.....{As such], the disclosure meets the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention." (emphasis added).

Thus, the genus of nucleic acids with at least 95-99% sequence identity to SEQ ID NO:356, which possess the functional property of enhancing glucose or FFA (free fatty acids) uptake by adipocyte cells, and would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description. Example 158, (page 530) of the present application provides detailed protocols for the glucose or FFA (free fatty acids) uptake assay by adipocyte cells including the extensive step-by-step guidance in the specification. Applicants claim only

those nucleic acids encoding proteins which meet both recitations of the claims, structural and functional. Further, the instant specification provides methods for determining percent identity between two nucleic acid sequences and teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. From the specific activity of the claimed nucleic acids encoding the PRO1182 polypeptide, the description of the claimed genus is achieved. Accordingly, one skilled in the art would have known that Applicants had knowledge and possessed the claimed nucleic acids with 95-99% sequence identity to SEQ ID NO: 356.

Hence, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C64**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 13, 2006

By: _____

Ginger R. Dreger
Reg. No. 33,055

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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